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In Focus

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1. *NTHL1* Mutation Causes Adenomatous Polyposis and Colorectal Cancer

Patients with adenomatous polyposis have higher risk for colorectal cancer; however causative genes remain unknown in a considerable fraction of these patients. On behalf of his collaborators, Robbert Weren (Nijmegen, Netherlands) presented whole-exome sequencing data from 51 individuals (of 48 families) with adenomatous polyposis. They identified a homozygous germline nonsense mutation in the base-excision repair (BER) gene *NTHL1* in 7 affected individuals from 3 unrelated families. These patients were homozygous for the germline mutation, and showed recessive inheritance of the adenomatous polyposis phenotype, whereas in controls, this mutation was only found in a heterozygous state. Thus, this new *NTHL1* gene mutation predisposes the homozygous individuals to a novel subtype of BER-associated adenomatous polyposis and colorectal cancer.

2. Whole Genome Sequencing Profiling in Autism

Previous genetic studies have identified hundreds of susceptibility loci for autism spectrum disorder (ASD). In this presentation, Ryan Yuen (Toronto, Canada) and his collaborators used whole-genome sequencing of 85 quartet families (parents and two ASD-affected siblings), consisting of 170 individuals with ASD, to generate a comprehensive data resource encompassing all classes of genetic variation and accompanying phenotypes of ASD. They found that more than two-thirds of the affected siblings carried different ASD-relevant mutations. These siblings with discordant mutations tended to demonstrate more clinical variability than those who shared a risk variant. This study reiterates that ASD is genetically heterogeneous, and whole-genome sequencing is necessary to delineate all genic and nongenic susceptibility variants in research and in clinical diagnostics. The study has been expanded to include 200 additional ASD families, and results are awaited.

3. Genome-wide Association Study Reveals Genetic Involvement with Diabetic Neuropathic Pain

Neuropathic pain affects around 1 in 4 diabetic patients in the UK, however genetic contributors are unknown. Here, Weihua Meng (Dundee, UK) and colleagues investigated the genetic information and the prescription records of 6927 diabetic individuals from the Genetics of Diabetes Audit and Research Tayside (GoDARTS) project. Cases of neuropathic pain were defined as diabetic patients with a multiple prescription history of one or more drugs specific for neuropathic pain (duloxetine, gabapentin, pregabalin, capsaicin cream/patch and lidocaine patch), and controls were diabetic individuals who were not prescribed any of these drugs, nor amitriptyline, carbamazepine, or nortriptyline. The authors identified 961 diabetic neuropathic pain cases and 3260 diabetic controls. Genome-wide association analyses revealed a cluster in the Chr1p35.1 (ZSCAN20-TLR12P) at rs71647933 in female patients, and a cluster in the Chr8p23.1 next to HMGB1P46 at rs6986153 in male patients, which were associated with neuropathic pain. This study provides evidence for sex-specific, genetic involvement with diabetic neuropathic pain.

4. *MCEMP1* Expression as a Stroke Biomarker

Stroke is a leading cause of death and functional disability, and a rapid blood-based diagnostic test may expedite diagnosis and prognosis of acute stroke. As part of the INTERSTROKE study, Kripa Raman from Guillaume Pare's group (Hamilton, Canada) assessed 302 stroke case and controls for transcriptome-wide peripheral blood gene expression using the Illumina HumanRef-8 v4 bead chip. Significantly expressed genes were validated using qPCR in another cohort of 62 individuals. The authors found that *MCEMP1* gene expression was sufficient to distinguish between stroke cases and controls (AUC = 0.812), and also differentiated between ischemic and hemorrhagic stroke cases (AUC = 0.783). Furthermore, *MCEMP1* expression was significantly associated with 1-month outcome, measured as Modified Rankin Score (MRS), after adjustment for available risk factors, primary stroke type and baseline MRS. Peripheral blood expression of *MCEMP1* may have utility as a diagnostic test for acute stroke, in distinguishing ischemic stroke from intracerebral hemorrhage and a prognostic biomarker of outcome.

5. *MTRNR2L12* as a Marker of Early Dementia in Down Syndrome

It has been reported that autopsied brain tissues of adult patients with Down syndrome contain histological changes identical with those observed in Alzheimer's disease. Interestingly, many adults with Down syndrome never present with dementia, whereas in some others, Alzheimer's disease-like dementia develops in the fifth decade of life. Miroslaw Bik-Multanowski (Krakow, Poland) and his collaborators performed cognitive assessment in a cohort of 48 adults with Down syndrome, with subsequent microarray-based analysis of whole-genome expression in leukocytes. Microarray data analysis revealed significant differences between groups of younger patients with severe cognitive disability and older patients without dementia with regard to expression of *MTRNR2L12* gene, which is known to be associated with Alzheimer's disease. These findings suggest a protective role of *MTRNR2L12* in the development of early Alzheimer's disease-like

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dementia in adults with Down syndrome. Further studies are warranted to evaluate potential usefulness of this marker in patients with Alzheimer's disease.

6. NGS Panel for Diagnosis of Early and Severe Forms of Polycystic Kidney Disease

Polycystic kidney disease (PKD) is one of the most common potentially life-threatening human genetic disorders, and early and severe PKD occur in patients with the autosomal recessive form (ARPKD) and 2–5% of the autosomal dominant form (ADPKD). PKD is highly genetically heterogeneous, making genetic testing difficult. Carsten Bergmann (Ingelheim, Germany) and colleagues have developed a novel customized sequence capture-based NGS panel for PKD that targets 95 genes. The authors analyzed a cohort of 308 patients with early and severe PKD, and found that the majority of patients carried mutations in *PKD1*, *PKD2* and *PKHD1*, however a subgroup harbored mutations in genes related to other ciliopathies (e.g., nephronophthisis, Joubert, Meckel, and Bardet–Biedl syndrome). They demonstrated that *PKD1* is a driver for early and severe manifestations in families with ADPKD. Notably, mutations in both ADPKD genes (*PKD1* and *PKD2*) can also be identified in ARPKD patients. The authors proposed a dosage-sensitive model for early and severe forms of PKD, and their NGS panel allows parallel analysis of all disease genes including *PKD1* which plays a decisive role in cyst initiation. An accurate genetic diagnosis is crucial for genetic counseling, prenatal diagnostics and the clinical management of patients.